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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1645	32

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/905,293	Yelton et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 20, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-6 and 8-52* is/are pending in the application.

4a) Of the above, claim(s) *23-27 and 32-52* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-6, 8-22, and 28-31* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 02/20/03 (paper no. 31) in response to the non-final Office Action mailed 08/14/02 (paper no. 29). With this, Applicants amended the specification.

Status of Claims

2) Claim 7 has been canceled via the amendment filed 02/20/03.

Claims 2-6 have been amended via the amendment filed 02/20/03.

Claims 1-6 and 8-52 are pending in the instant application.

Claims 1-6, 8-22 and 28-31 are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Maintained

5) The objection to the drawings made in paragraph 6 of the Office Action mailed 08/14/02 (paper no. 29) is maintained for reasons set forth therein.

Objection(s) Withdrawn

6) The objection to the specification made in paragraph 7 of the Office Action mailed 08/14/02 (paper no. 29) is withdrawn in light of Applicants' amendment to the specification.

Rejection(s) Moot

7) The rejection of claim 7 made in paragraph 12(d) of the Office Action mailed 08/14/02 (paper no. 29) under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

8) The rejection of claim 7 made in paragraph 14 of the Office Action mailed 08/14/02 (paper no. 29) under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is

moot in light of Applicants' cancellation of the claim.

Rejection(s) Withdrawn

9) The rejection of claim 6 made in paragraph 12(a) of the Office Action mailed 08/14/02 (paper no. 29) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

10) The rejection of claims 1-3, 5 and 6 made in paragraph 12(b) of the Office Action mailed 08/14/02 (paper no. 29) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

11) The rejection of claims 5 and 6 made in paragraph 12(c) of the Office Action mailed 08/14/02 (paper no. 29) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

12) The rejection of claims 8-10, 15-22 and 29-31 made in paragraph 12(e) of the Office Action mailed 08/14/02 (paper no. 29) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims and/or the base claim(s).

13) The rejection of claims 1-3, 5, 8-22 and 28-31 made in paragraph 13 of the Office Action mailed 08/14/02 (paper no. 29) under 35 U.S.C § 112, first paragraph, with regard to the written description, is withdrawn in light of Applicants' amendment to the claims and/or the base claim(s).

Rejection(s) Maintained

14) The rejection of claims 1-6, 8-22 and 28-31 made in paragraph 14 of the Office Action mailed 08/14/02 (paper no. 29) under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is maintained therein and herebelow.

Applicants argue that the definition on page 9 describes that 'inhibiting immunoglobulin-induced toxicity' means to reduce or alleviate symptoms generally associated with toxicity caused by immunoglobulin or Ig fusion therapy. Applicants further elaborate that the invention is directed to altering an immunoglobulin to inhibit (including reducing and alleviating) the toxicity resulting from administration thereof, as compared to the toxicity resulting from administration of the unaltered immunoglobulin.

Applicants' arguments have been carefully considered, but are non-persuasive. In order to 'reduce or alleviate symptoms' one has to treat a subject who already has the symptoms. By

administering a CH2 domain-altered antibody to a subject who does not have symptoms of immunoglobulin-induced toxicity , one can only avoid the development of such symptoms. The claimed method 'for inhibiting immunoglobulin-induced toxicity *resulting* from immunoglobulin immunotherapy in a subject' is not the same as a method of administering an immunoglobulin to a symptomless subject, said immunoglobulin having a variable region and a constant region and being modified prior to administration by structurally altering multiple toxicity-associated regions in the CH2 domain such that toxicity associated with the immunoglobulin is reduced or alleviated in said subject to whom the modified immunoglobulin is administered. The showing in the instant specification, especially Example 3, is limited to just that.

New Rejection(s)

Applicants are asked to note the following new rejection(s) made in this Office Action. The new rejections are necessitated by Applicants' amendments to the claims and/or the base claim(s).

Rejection(s) under 35 U.S.C. § 102

15) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> **(e)** The invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

16) Claims 1, 2, 5 and 8-10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Morgan *et al.* (WO 94/29351, already of record).

The claimed method is interpreted as a method of administering to a subject a structurally altered immunoglobulin molecule which has a variable region and a constant region wherein the structural alteration is in the multiple toxicity-associated regions of the CH2 domain of said immunoglobulin. It is noted that none of the claims under examination identify the "multiple toxicity-associated domains in the constant region" as containing any specific regions of the CH2 domain, such as, C-terminal and N-terminal regions of the CH2 domain, or regions of the CH2 domain comprising amino acids 231-238 and amino acids 310-331. It is further noted that as acknowledged by Applicants in the first full paragraph on page 3 of the Appeal Brief, alterations in

multiple amino acids in a single toxicity-associated domain in the constant region, or alterations by single or multiple mutations, such as, amino acid insertions and substitutions in the CH2 domain are encompassed within the scope of the instant invention as well. See also lines 21 and 22 on page 4 of the specification.

Morgan *et al.* disclosed methods of treating diseases in which antibody or immunoglobulin therapy leads to undesirable toxicity or ADCC due to antibody-mediated complement fixation comprising administering to a human or animal subject an altered or modified antibody (having a variable and a constant region), wherein one or more amino acid residues in the CH_2 domain of the antibody are altered such that the ability of the antibody to fix complement is altered as compared to unaltered antibody (see pages 5 and 12). "The constant region of the antibodies to be altered according to the invention may be of animal origin and is preferably of human origin. It may also be of any isotype" (i.e., IgG, IgM or IgA), "but is preferably human IgG and most preferably human IgG1" (see page 6, first paragraph). These antibodies can be natural antibodies, chimeric antibodies, CDR-grafted antibodies or humanized antibodies (see page 13). The altered antibodies can be produced recombinantly (see page 13). The alteration in the constant region of the antibody can be produced by site directed mutagenesis (see page 14). The ability of the resultant antibody with altered constant region to fix complement or mediate ADCC, is substantially reduced (see page 6, fifth paragraph and page 7). Morgan *et al.* further taught an antibody "which fully retains its immunosuppressive properties but which has substantially reduced toxicity". The antibody is tolerated *in vivo* (see page 7). The alteration may comprise substitution, replacement, insertion or deletion of one or more amino acid residues (see page 9). For example, Morgan *et al.* taught an antibody molecule having an alteration at 243 and being unable to mediate ADCC, and an IgG4 having the Leu235 to Glu alteration with abrogated ADCC. Changing the glycine at 237 to alanine of IgG1 also abolished FcR1 binding and reduced complement fixation and FcRIII mediated function. Alteration of the whole regions 233, 234, 235 and 236 (i.e., multiple regions or multiple amino acids) by exchanging with the sequence found in IgG2 abolished multiple functional properties, such as, FcR1 binding **and** complement fixation, and reduced FcRIII mediated function of IgG1 (pages 37 and 40). The alteration in the CH_2 domain of the antibody while altering the ability to fix complement can **additionally** inhibit the binding to FcR1 receptors (see page 8).

Specific alterations at specific amino acid positions result in altered human antibodies with potent immunosuppressive ability with minimal (i.e., reduced) toxicity (see page 9). Therapeutic and pharmaceutical uses of these altered immunoglobulins are taught in therapy and diagnosis of diseases (see pages 10 and 11). Examples of a variety of immunological diseases and conditions which can be treated with antibodies or immunoglobulins with the altered constant region are disclosed including cancer immunotherapy (see page 12). For instance, the composition comprising the altered immunoglobulin is used in methods of therapy and diagnosis comprising "administering an effective amount" to a "human or animal subject" in therapeutic doses of 0.1-25 mg/kg body weight. The composition is used in the immunotherapy of many conditions including cancer and GI tract disease (see entire page 12) "without producing any significant adverse toxic effects", such as those mediated via complement fixation (see page 1). Thus, a method of *in vivo* administration to a subject of an antibody structurally altered in multiple toxicity-associated regions of the CH2 domain wherein the antibody exerts minimal or no immunoglobulin-associated toxicity was disclosed by Morgan *et al.*

Claims 1, 2, 5 and 8-10 are anticipated by Morgan *et al.*

17) Claims 1-6, 8, 11, 13-15, 17-19, 21, 22 and 28-31 are rejected under 35 U.S.C. § 102(e) as being anticipated by Yelton *et al.* (US 5,792,456, already of record).

Yelton *et al.* disclosed a monoclonal antibody BR96 produced by the hybridoma HB10036, and a ChiBR96 produced by the hybridoma HB10460, both deposited at the ATCC (see column 1 and 2). Note that the antibodies recited in instant claims 13, 14, 17, 18, 21 and 22 have the same ATCC accession numbers as that of Yelton's. A mutant BR96 is also taught (see column 7). It is disclosed that BR96 recognizes and binds Le^y or Lewis Y antigen (see column 1). A fusion protein of the mutant BR96 which can be used to treat human carcinoma is taught (see column 10). It is disclosed that BR96 can be used as a fusion protein, or as a mutant IgG, or mutant Fab, or mutant $F(ab')_2$, or as an immunoconjugate after conjugating it to a cytotoxic agent such as doxorubicin or a therapeutic agent such as *Pseudomonas* exotoxin A (see column 11). Preclinical studies done with such a conjugate are discussed (see column 2). Yelton *et al.* teach BR96 or mutant BR96 conjugated to a cytotoxic agent selected from the group consisting of antimetabolites, ankylating agents, anthracyclines, antibiotics, anti-mitotic agents and chemotherapeutic agents (see claims 29

and 30). It is taught that "because of the toxin or drug, the conjugate is more potent than non-conjugated mutant BR96" (see column 12). Explicitly taught are functional equivalents of mutant BR96 antibody that do **not** include the Fc region, i.e., mutant BR96 Fab or $(Fab')_2$ lacking CH2 domain, exhibit ADCC or CDC properties (see column 20, lines 51-53). The antibody can be administered *in vivo* and can be conjugated or linked to a therapeutic drug or toxin for delivering the therapeutic agent to the site of the carcinoma (see column 20). It is taught that introduction of mutations to BR96 did not adversely affect tumor specificity nor significantly increase binding to normal tissues (see column 35). Thus, the BR96 antibody with multiple mutations (see Example 6) and mutant BR96 lacking CH2 domain and not exhibiting ADCC or CDC properties are taught. Since the prior art mutant BR96 Fab used in Yelton's method qualifies as a CH2-deleted (structurally altered) immunoglobulin, the disclosure of Yelton *et al.* anticipates the instant invention. That the prior art mutant BR96 Fab or $(Fab')_2$ is not associated with immunoglobulin-induced toxicity is inherent from Yelton's disclosure because Yelton *et al.* teach that Fab molecule is devoid of CH2 domain (see lines 41-44 in column 6). The absence of CH2 domain in the prior art antibody inherently renders it incapable of mediating antibody-dependent cellular cytotoxicity response or activating complement.

Claims 1-6, 8, 11, 13-15, 17-19, 21, 22 and 28-31 anticipated by Yelton *et al.*

18) Claims 1, 3, 5, 12, 16 and 20 are rejected under 35 U.S.C. § 102(b) as being anticipated by Gundel *et al.* (WO 93/02702).

Gundel *et al.* taught a method of administering to an asthma patient Fab or F(ab)2 fragments of an antibody that binds to Lewis X antigen-containing ELAM-1 receptor. The antibody used can be humanized chimeric antibody (see claims 1-3 and 8-11; last half of page 7 and 6). Gundel's Fab or F(ab)2 antibody fragment is viewed as the same as the Applicants' CH2-deleted immunoglobulin. The absence of CH2 domain in the prior art antibody inherently renders it incapable of mediating antibody-dependent cellular cytotoxicity response or activating complement.

Claims 1, 3, 5, 12, 16 and 20 are anticipated by Gundel *et al.*

Remarks

19) Claims 1-6, 8-22 and 28-31 are under examination.

20) Applicants' amendment necessitated the new ground(s) of rejection presented in this Office

action. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

22) Any inquiry concerning this communication or earlier communication(s) from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail service. The Examiner can normally be reached on Monday to Friday from 7.15 a.m to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

S. DEVI, PH.D.
PRIMARY EXAMINER

May, 2003